Removing Barriers to the Inclusion of Patients with Renal Impairment in Clinical Trials

ACT AEC Accelerating Clinical Trials / Accélérer les Essais Cliniques

UNIVERSITY OF ALBERTA

ACT Meeting
Sydney, Nova Scotia
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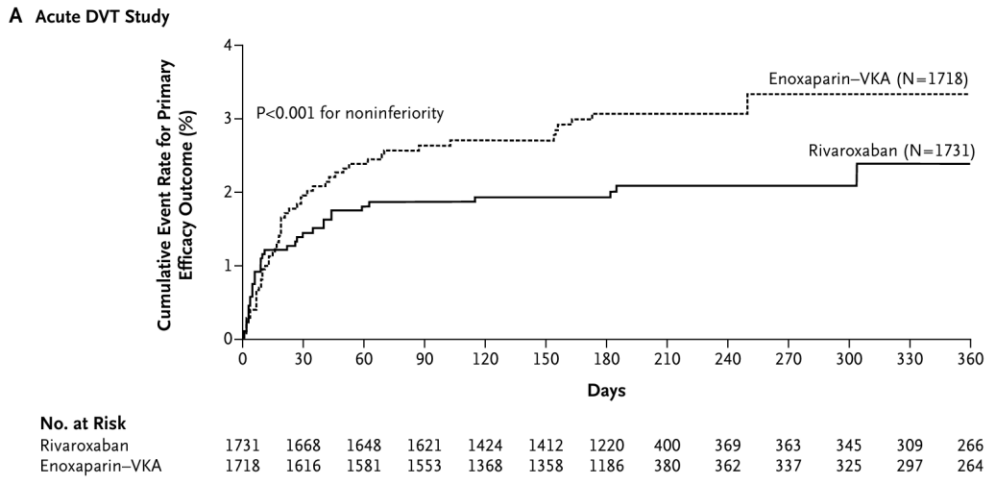
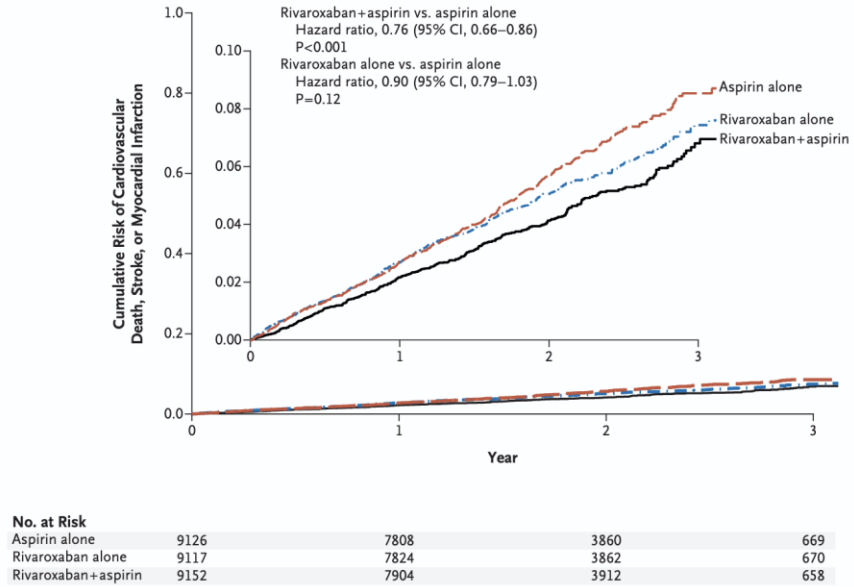
Rivaroxaban

Product monograph: not recommended if CrCl<15

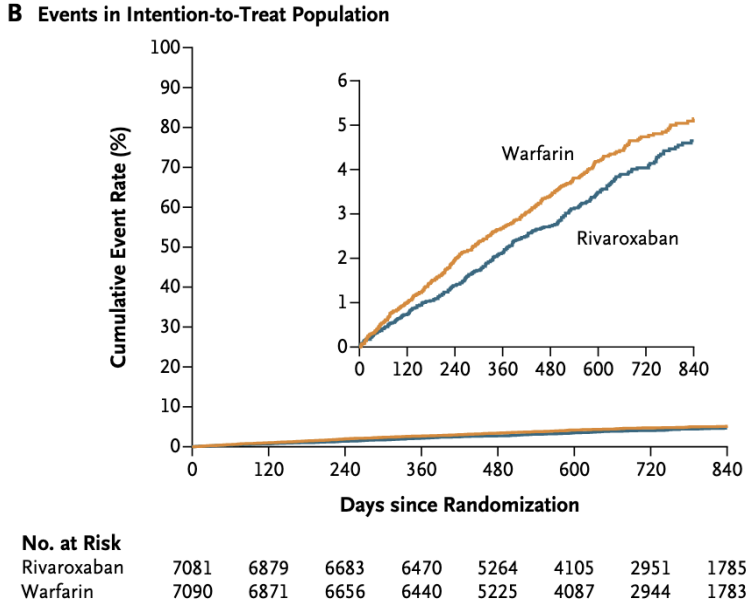
TRACK: NCT03969953
RENAL-AF: NCT02942407
SAFE-D: NCT03987711



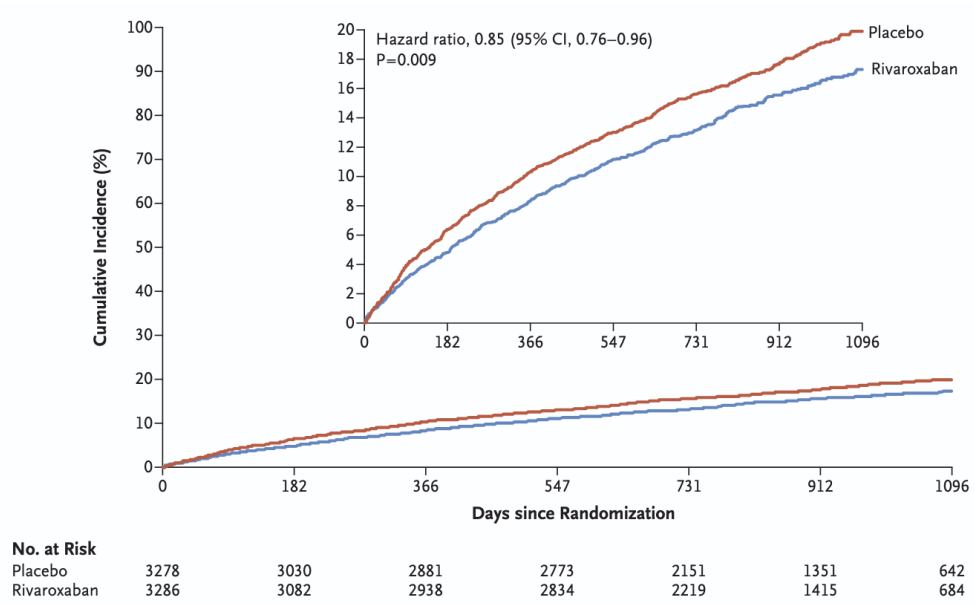
EINSTEIN NEJM 2010;363:2499510



COMPASS NEJM 2017;377:1319-1330



ROCKET AF NEJM 2011;365:883-91



VOYAGER PAD NEJM 2020;382:1994-2004

Chronic Kidney Disease

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, Glomerular filtration rate (GFR) category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

KI 2024 105 (Suppl 4S), S117–S314

CrCl/eGFR equations:
1) Cockgroft Gault
2) MDRD
3) CKD-EPI 2009, 2012, 2021
4) EKFC 2024

GFR determinants:
Biomarkers (Cr, CysC)

Non-GFR determinants:
Age
Sex/Gender
Race

CKD is Common (10-15% of the population)

Table 1. Mean prevalence of CKD split by geographical region with 95% Confidence Intervals.

	Stage 1 to 5		Stages 3 to 5	
	N*	Prevalence (%)	N*	Prevalence (%)
S Africa, Senegal, Congo	5,497	8.66 (1.31, 16.01)	1,202	7.60 (6.10, 9.10)
India, Bangladesh	1,000	13.10 (11.01, 15.19)	12,752	6.76 (3.68, 9.85)
Iran	17,911	17.95 (7.37, 28.53)	20,867	11.68 (4.51, 18.84)
Chile	0	NONE	27,894	12.10 (11.72, 12.48)
China, Taiwan, Mongolia	570,187	13.18 (12.07, 14.30)	62,062	10.06 (6.63, 13.49)
Japan, S Korea, Oceania	654,832	13.74 (10.75, 16.72)	298,000	11.73 (5.36, 18.10)
Australia	12,107	14.71 (11.71, 17.71)	896,941	8.14 (4.48, 11.79)
USA, Canada	20,352	15.45 (11.71, 19.20)	1,319,003	14.44 (8.52, 20.36)
Europe	821,902	18.38 (11.57, 25.20)	2,169,183	11.86 (9.93, 13.79)

*N is number of participants in the sample estimate.

PLoS One 2016 Jul 6;11(7):e0158765

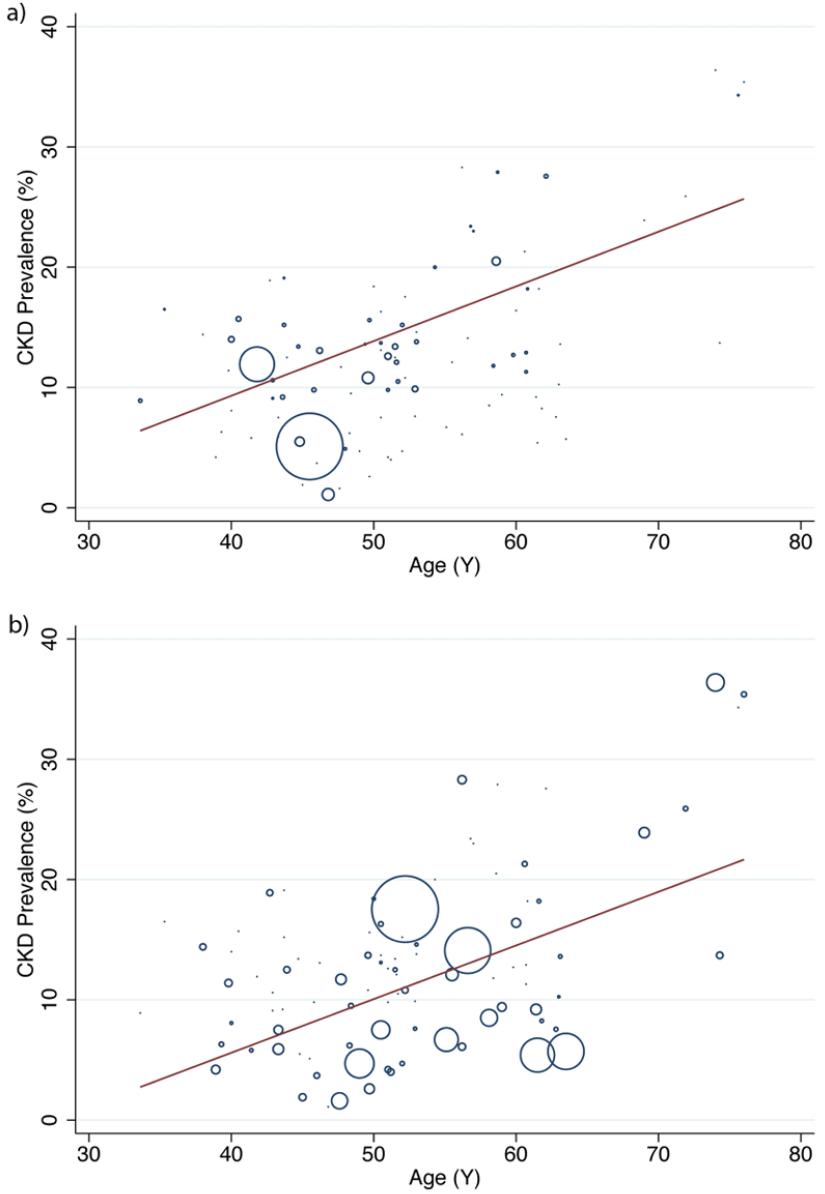


Fig 3. Meta Regression of CKD Prevalence and mean sample population age (a) Studies reporting stages 1 to 5 (b) Studies reporting stages 3 to 5. Each circle represents a study prevalence estimate with the size denoting the precision of the estimate.

Goals of Increasing Diversity in Clinical Trials.

Goal	Key Challenges	Implications
Building trust in medical research and institutions	Distrust of medical and scientific professions can be an important obstacle to receiving effective medical care.	The effect on public trust of the design and conduct of clinical trials can be as important to public health as trials' results. Investments should be made in elucidating how clinical trial practices affect public trust.
Promoting fairness for potential participants and their communities 	Opportunities to participate in trials are limited. Preferences, resources, and trust all affect willingness to participate in trials. Health systems' capacities to conduct trials vary among communities.	Overcoming unjust barriers to participation for disenfranchised groups will require affirmative outreach and recruitment actions. Grading trials on inclusive outreach and recruitment practices, rather than solely enrollment demographics, may better reflect recruitment equity. Investing in trial capacity in marginalized communities may benefit such communities broadly by improving adoption of innovations.
Generating biomedical knowledge 	Sample sizes are often too small to permit assessment of treatment efficacy within particular subgroups. Clinically significant differences in treatment efficacy between groups that are underrepresented and those that are overrepresented in trials may not be common. Efforts to diversify trials address only some of the barriers to efficient patient recruitment.	Investigators should acknowledge that more inclusive trials may not show whether a treatment is effective for certain patient subgroups or meaningfully shift estimates of the treatment's efficacy. Shifting the focus of trials to diseases that disproportionately affect marginalized groups may more effectively generate knowledge benefiting these groups. Future meta-research could clarify the importance and detectability of heterogeneous treatment effects.

NEJM 2023;388:1252-1254

Why do we have eligibility criteria in clinical trials?

- To define and standardize clinical trial populations
  - Representativeness
  - Generalizability
- To improve statistical power
  - Enrich the study population re: benefits/risks, adherence, competing risks
  - Minimize drug discontinuation
- Safety of participants
  - PK, PD, drug-drug interactions, teratogenicity, comorbidities, AEs/SAEs

Clinical Trials: A Practical Approach 1st Edition: July 17, 2013

Patients with CKD and Underrepresented in RCTs

- Coronary artery disease
- Cardiovascular disease
- Peripheral arterial disease
- HFrEF
- Cancer
- COVID-19
- Many, many more settings

KI 2006 70, 2021–2030

JAMA Intern Med. 2016 Jan;176(1):121-4
JAMA Network Open. 2024;7(3):e240427

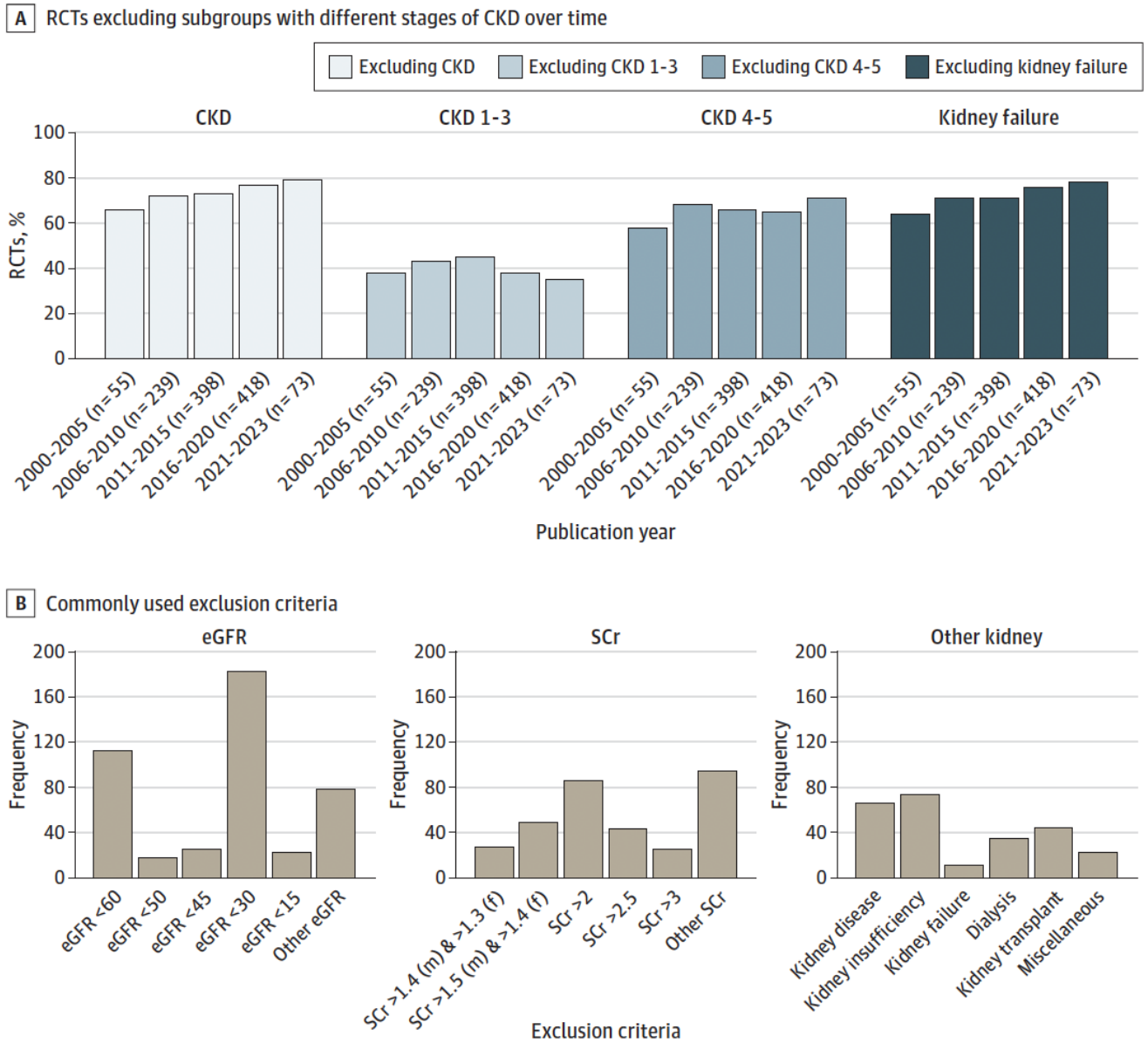
CJASN 2019 Dec 30;15(1):117–119

Curr Probl Cardiol 2023 Mar;48(3):101047

JAMA 2018 Jun 19;319(23):2437-2439

JASN 31: 2250–2252, 2020

Figure 1. Overview of Exclusion of Patients With Chronic Kidney Disease (CKD) From Cardiovascular Randomized Clinical Trials (RCTs)



JAMA Network Open
2024;7(3):e240427

Table 1. Characteristics of Randomized Clinical Trials of Anticancer Drugs Examined for the Exclusion of Patients With Chronic Kidney Disease (continued)

	Trials, No. (%)	Patients, No.	Trials Explicitly Excluding Kidney Disease, No. (%)	*P* Value[a]
Cancer type				
Bladder	4 (1)	959	3 (75)	.45
Breast	111 (36)	144 052	87 (78)	
Colorectal	52 (17)	42 619	48 (92)	
Lung	96 (31)	50 175	86 (90)	
Prostate	47 (15)	45 084	40 (85)	
Intervention type				
Chemotherapy	78 (25)	60 986	68 (87)	.02
Biologic or immunotherapy	87 (28)	81 802	78 (90)	
Endocrine therapy	31 (10)	65 331	18 (58)	
Targeted agents	84 (27)	43 725	78 (86)	
Other therapy	30 (10)	31 045	28 (93)	
Trial phase				
2	55 (18)	11 094	45 (82)	.82
2/3	7 (2)	7610	7 (100)	
3	246 (79)	263 735	210 (85)	
4	2 (1)	440	2 (100)	
Funding source				
Industry	208 (67)	168 941	177 (85)	.61
Government	39 (13)	32 634	34 (87)	
Both	63 (20)	81 314	53 (84)	
Journal				
JAMA	4 (1)	6287	3 (75)	.09
Journal of Clinical Oncology	137 (44)	113 495	124 (91)	
Journal of the National Cancer Institute	5 (2)	4786	4 (80)	
Lancet	16 (5)	36 465	12 (75)	
Lancet Oncology	112 (36)	80 233	90 (80)	
New England Journal of Medicine	36 (12)	41 623	31 (86)	

Table 2. Thresholds Used for Exclusion of Patients With Kidney Disease in Randomized Clinical Trials of Anticancer Drugs (N = 264 Trials)[a]

Measurement for Kidney Function–Based Exclusion[a]	No. of Trials (%)[b]
Serum creatinine value	162 (62)
Serum creatinine value relative to ULN	129 (49)
>ULN	16 (6)
>1.25-times ULN	7 (3)
>1.5-times ULN	93 (35)
>2-times ULN	6 (2)
>2.5-times ULN	6 (2)
>5-times ULN	1 (0.4)
Absolute serum creatinine value, mg/dL	33 (13)
>1.5	17 (6)
>2.0	15 (6)
>4.0	1 (0.4)
CrCl, mL/min	115 (44)
<60	38 (14)
<50	44 (17)
<45	10 (4)
<40	12 (5)
<30	11 (4)
eGFR, mL/min/1.73 m^2	14 (5)
<60	5 (2)
<50	4 (2)
<45	1 (0.4)
<30	4 (2)
Proteinuria	31 (12)
Nonspecified renal exclusion[c]	41 (16)
Multiple exclusion criteria related to kidney function[d]	90 (34)

JAMA 2018 Jun 19;319(23):2437-2439

Why are Patients with CKD Underrepresented in RCTs?

Systematic exclusion

- Comorbidities
- Safety concerns
- Competing risks
- Polypharmacy

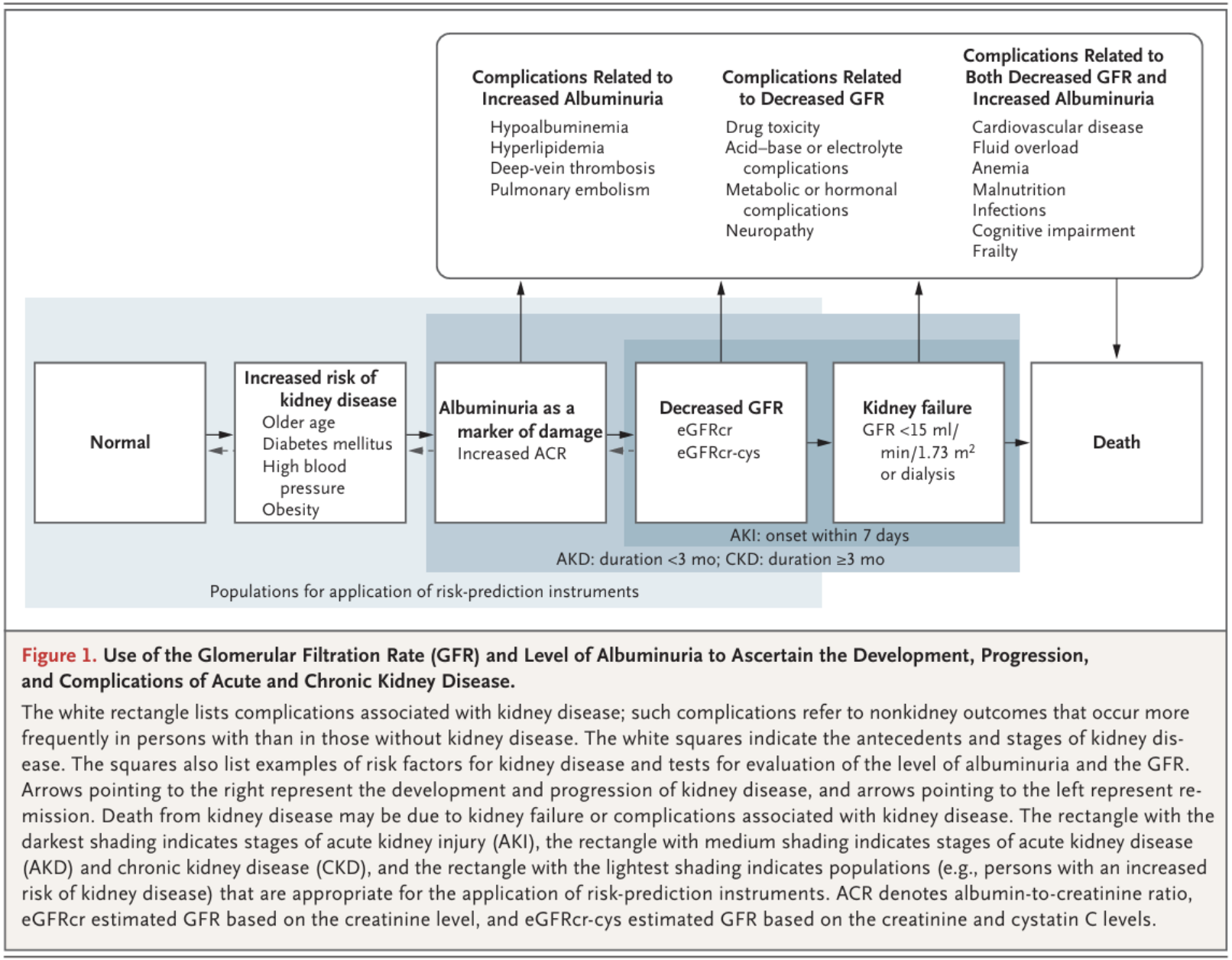


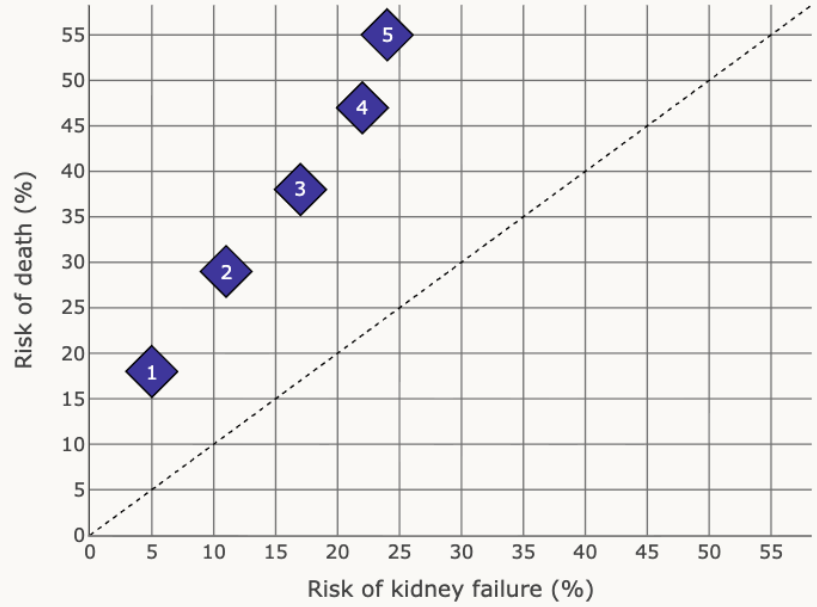
Figure 1. Use of the Glomerular Filtration Rate (GFR) and Level of Albuminuria to Ascertain the Development, Progression, and Complications of Acute and Chronic Kidney Disease.

The white rectangle lists complications associated with kidney disease; such complications refer to nonkidney outcomes that occur more frequently in persons with than in those without kidney disease. The white squares indicate the antecedents and stages of kidney disease. The squares also list examples of risk factors for kidney disease and tests for evaluation of the level of albuminuria and the GFR. Arrows pointing to the right represent the development and progression of kidney disease, and arrows pointing to the left represent remission. Death from kidney disease may be due to kidney failure or complications associated with kidney disease. The rectangle with the darkest shading indicates stages of acute kidney injury (AKI), the rectangle with medium shading indicates stages of acute kidney disease (AKD) and chronic kidney disease (CKD), and the rectangle with the lightest shading indicates populations (e.g., persons with an increased risk of kidney disease) that are appropriate for the application of risk-prediction instruments. ACR denotes albumin-to-creatinine ratio, eGFRcr estimated GFR based on the creatinine level, and eGFRcr-cys estimated GFR based on the creatinine and cystatin C levels.

NEJM 2022;386:2120-8

Competing risks

Risk predictions at years 1 to 5 from the diagnosis of moderate or severe CKD



Each diamond represents the values of the risk of death (y axis) and kidney failure (x axis) at years 1 to 5. Note that people with kidney failure may die within the prediction timeframe.

https://kdpredict.com/

Age in years

65

Sex at birth

Male

CKD-EPI eGFR formula

2009 | 2021

eGFR (mL/min/1.73m2)

25

Measure of proteinuria

ACR | PCR | Dipstick

Units

mg/g | mg/mmol

ACR (mg/mmol)

50

Model

4 variables | 6 variables

Diabetes

Cardiovascular disease

Update risk

Renalism within ACT???

JASN 2004;15:2462-8

RFA #1: High Impact RCTs

- ACHIEVE = dialysis
- ARTESIA: SCr>221 or CrCl<25
- B-Free: none
- CLEAR: CrCl<30
- COP-AF: eGFR<30
- CYCLE: none
- EnAKT = living kidney donation
- HEMOTION: none
- RAFF4: none
- REVISE: none
- REFINE-ICD: CRF (HD or PD)

RFA #2: Conduct of RCTs

- ALICE: Pre-existing CRI
- CRAVE: eGFR<30
- Dial-Bicarb: dialysis
- KidneyCareOutreach: CKD
- NAPTEM-C: eGFR<60
- OK-TRANSPLANT 1: CKD/dialysis
- SAFE-AFIB: none
- TheRAPy: none
- VICTORY: none

RFA #3: Biotechnology

- AMT-143: clinically significant abnormal lab test
- EQUAL Dialysis: dialysis
- LEADS: none
- PERIOP-06: none
- PONTIAC: AKI
- PVC-RAM-2: none

RFA #5: Bringing Trials to Canada

- ARTS: eGFR<30
- BEAT-Calci: dialysis
- BELIEVERS: ???
- CRAAFT-HF: none
- EASThigh: none
- IMPROVE-AD: none
- MAC-HF: none
- SURFSUP: none
- The 3LTA Study: none
- T4P: none

clinicaltrials.gov and anzctr.org.au and isrctn.com

	Population	Intervention	Primary Outcome	Exclusion criteria
ARTESIA	Subclinical AF	**Apixaban** vs ASA	Stroke or systemic embolism	SCr>221 or CrCl<25
CLEAR	Post-MI	**Colchicine** vs placebo **Spironolactone** vs placebo	**CV death, MACE**	CrCl<30
COP-AF	Non-CV thoracic surgery	**Colchicine** vs placebo	**AF, MINS**	eGFR<30
REFINE-ICD	Prior MI, LV dysfunction, abnormal ECG	**ICD** vs medical therapy	**Mortality**	CRF (HD or PD)
ALICE	Laceration repair in children	IN dexmedetomidine vs IN midazolam vs IN NO	OSBD-R (distress)	Pre-existing CRI
CRAVE	Right heart failure	**Empagliflozin** vs ranolazine vs standard of care	Feasibility outcomes	eGFR<30
NAPTEM-C	Age>50 or age>18 with a high-risk medical condition or immunosuppression SARS-CoV-2 infection	**Paxlovid** vs Antioxidant vs usual care Antioxidant vs usual	**All cause hospitalization or death**	eGFR<60
AMT-143	Unilateral open hernia repair	AMT-143 hydrogel containing ropivacaine vs ropivacaine vs placebo	**Safety, tolerability, PK**	clinically significant abnormal lab test
ARTS	Elective abdominal or pelvic surgery	**Apixaban** vs no OAC	VTE	eGFR<30

Strategies to Support Better Eligibility Criteria Enrollment

- Increasing Patient Involvement in Clinical Trial Design
- Re-examining Exclusion and Inclusion Practices
  - Justification based on internal validity, safety
- Increasing the Use of Innovative Trial Designs
  - Pragmatic trials
  - Basket trials
  - Adaptive trials

FDA: Evaluating Inclusion and Exclusion Criteria in Clinical Trials, April 2018

Modernizing Eligibility Criteria

Benefits

- Earlier access to IP
- Better safety and efficacy data
- Earlier identification of drugs that may not be effective
- Generalizability to “real-world” patients
- Faster recruitment

Risks

- More variability in outcomes (sample size implications)
- Safety concerns may require separate cohorts or stratified analyses
- Complicate attribution of AEs
- Increased costs associated with additional cohorts
- Potential for additional procedures for increased safety monitoring
- Additional resources required

FDA: Modernizing Eligibility Criteria November 2017

Broadening eligibility criteria in cancer RCTs

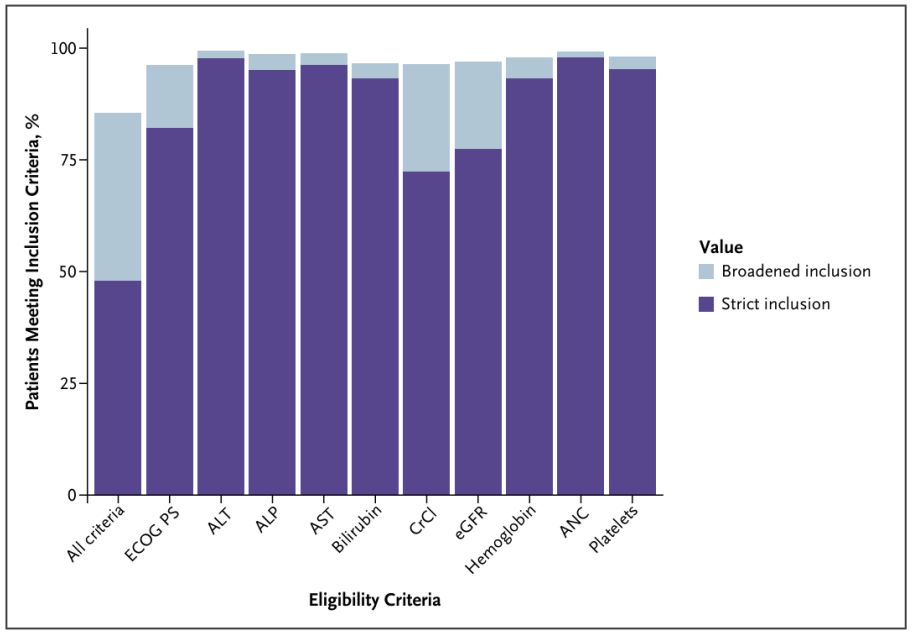


Figure 1. Proportion of All Weighted Patients Included by Trial Criteria.

Results are weighted to treat cancer types equally. ALP denotes alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; and eGFR, estimated glomerular filtration rate.

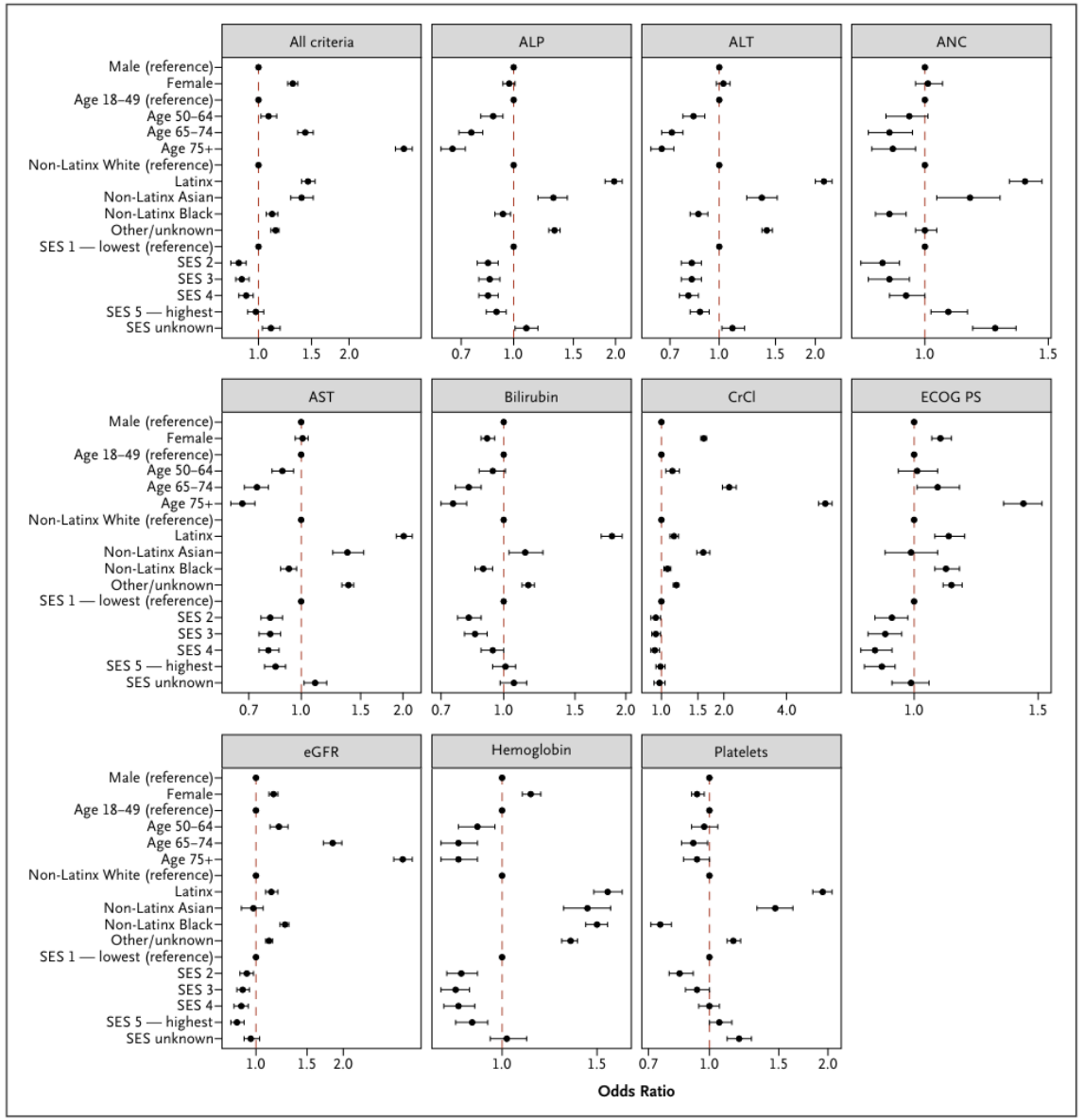


Figure 2. Odds of Exclusion by Strict Criteria by Sex, Age, Race or Ethnicity, and Area-Level Socioeconomic Status (SES).

Results are weighted to treat cancer types equally. An odds ratio greater than one indicates that the group has higher odds of exclusion by the strict criterion compared with the reference group. Age is in years. ALP denotes alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; and eGFR, estimated glomerular filtration rate.

NEJM Evid 2024;3(4)

FDA Guidance: The Need for PK in CKD/dialysis

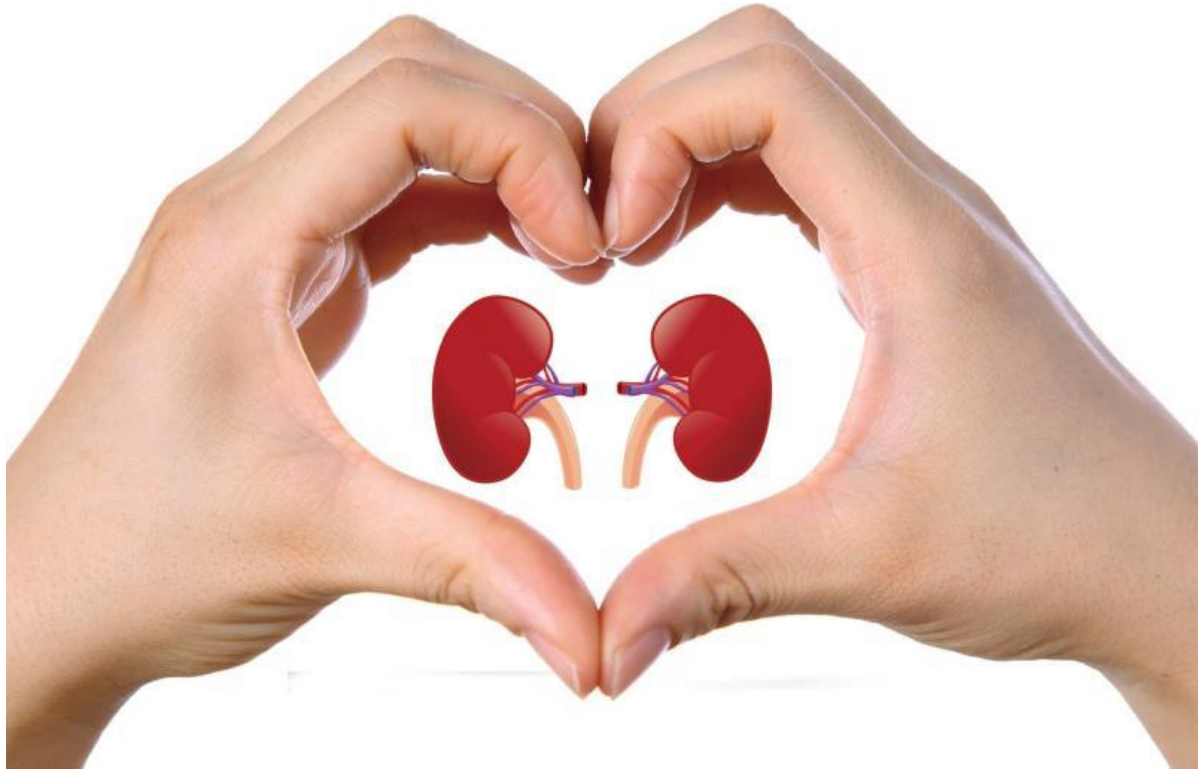
- The FDA recommends that PK be characterized early in drug development
  - Phase 1/2 studies or modeling /simulation strategies
  - Sequential/adaptive enrollment of patients with CKD can also be considered
  - Population PK analyses of phase 2/3 studies may be sufficient
- Inclusion of patients with CKD in the late-phase clinical studies
- A dedicated PK study is recommended when a drug or its active metabolites are thought to be substantially eliminated by the kidneys (kidney clearance of unchanged drug >30%)
- GFR >90, 60-90, 30-60, <30 categories with similar age, sex, race/ethnicity, weight and no drugs that potentially impact metabolism with sample sizes based on precise estimates of PK parameters
- Single dose PK is usually sufficient unless time dependent PK is anticipated
- Same dose across GFR as Cmax is not influenced by GFR
- Lower doses and/or less frequent administration in multiple dose studies

FDA: Pharmacokinetics in Patients with Impaired Renal Function March 2024

Conclusion

- CKD is common and affects 10-15% of the population
- Patients with CKD are underrepresented in clinical trials across acute/chronic diseases and therapeutic areas
- Exclusion based on kidney function may be justified when considering internal validity and safety
- Facilitators of the inclusion of patients with CKD in clinical trials include modernizing/broadening eligibility criteria, innovative designs and ensuring there is early PK data of IP during the drug development process

Thank You



CNTN|RCEN
Canadian Nephrology Trials Network
Réseau canadien d'essais cliniques en néphrologie

Canadian **VIGOUR** Centre
Bridging Hearts and Minds

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE